Régulation de la transcription et maladies génétiques

Rapport Hcéres

agence d'évaluation de la recherche
et de l'enseignement supérieur

Section des Unités de recherche

Evaluation report

Research unit:

Transcriptional regulation and genetic diseases

the University Paris 5

March 2009

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

mars 2009

Evaluation report

The research unit :

Name of the research unit : Transcriptional regulation and genetic diseases s

Requested label : UMR

N° in case of renewal : UPR 2228

Head of the research unit : M. Philippe DJIAN

University or school :

University Paris 5

Other institutions and research organization:

CNRS

Date of the visit :

6 February 2009

Members of the visiting committee

Chairman of the commitee:

M. Laszlo TORA, University of Strasbourg 1, France

Other committee members:

M. Ken CADIGAN, University of Michigan, USA

M. Bernard VERRIER, University of Saint Etienne, France

Ms. Cécile EGLY, University of Strasbourg 1 France

M. Serge BIRMAN, University of Paris 6 France

CNU, CoNRS, CSS INSERM, représentant INRA, INRIA, IRD.....) representatives :

Ms. Valérie SCHREIBER, CoNRS representative

Ms Chantal ASTIER, CNU representative

Observers

AERES scientific representative:

M. Philippe BOUVET

Research organization representatives :

Ms. Martine DEFAIS, CNRS

M. Bruno VARET, Université Paris 5

Ms Marie-Claude LABASTIE, Université Paris 5

Evaluation report

1 • Short presentation of the research unit

- Number of lab members : 28 including
  - 3 researchers with teaching duties
  - 8 full time researchers
  - 3 postdoctoral fellows
  - 5 PhD students, all funded
  - 9 engineers, technicians and administrative assistants

- Number of HDR: 10
- Number of PEDR: 2
- Number of students who have obtained their PhD during the past 4 years: 8
- Number of "publishing" lab members: 9 out of 11

2 • Preparation and execution of the visit

The visit was well prepared, with a thorough and detailed document provided in advance. On site, the visit was properly organized, with presentations and discussions with group leaders, technical and administrative staff, students and post-docs. The director gave his presentation in front of the committee and in the presence of the other members of the Unit. The committee had time to discuss various issues and the execution of the visit was good. No committee visit was organized to visit the different separate laboratories of the unit, situated at two different floors in the IFR.

3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

Overall, the research carried out at the unit can be qualified as good. The management of the unit is well done. The committee noticed a substantial heterogeneity in the performances in the various groups, yet the general feeling was rather positive. While some groups are rather at the international standard, others experience some difficulties to reach a level of visibility, which may be expected for an internationally competitive research unit in France. This is also visible when one considers the level of funding that various groups can attract into the institute as well as the recent track records of the PIs. While the unit as a whole published an impressive number of papers, very few appeared in high impact factor journals. It is surprising that such a small research unit, with only 30 members (divided in 5 groups), can function and stay more or less competitive internationally. The committee was surprised to learn that in the same building (IFR) 13 other units function also, some with similar or overlapping research thematic than the UPR2228.

It is also worth mentioning that in the past four years, the head of the unit was deeply involved in the administration of research also at the level of the IFR and this at a high degree. As a director of the unit UPR2228, he will start his third mandate. His administrative duties in the next four years will probably increase because he will also become the director of a new IFR. Thus, it seems that the director will have less time in the future to concentrate on the scientific and administrative duties of the unit and on his own group.

Regarding the educational aspect, the committee was glad to meet the 8 enthusiastic doctoral students and post-docs. It appears that PhD studies at the unit are well organized and supervised. The PhD students belong to three different doctoral schools. The committee notes that at some of the doctoral schools the tutorship is not well organized, since no thesis committees have been constituted.

4 • Specific appreciation team-by-team and/or project-by-project

Group 1: Chromatin, nuclear organization and regulation of gene expression

This team is headed by a CR1 CNRS and includes 1 post-doc and 1 technician (CNRS). One assistant professor and 1 post-doc will join the group in 2009. The committee acknowledges the high quality of the work performed by this small group and was convinced by the interest of the projects aimed to study the regulation of the expression of the IFNß gene by chromatin and nuclear organization. These projects are: to decipher the mechanisms regulating IFNß silencing by localisation to pericentromeric heterochromatin, to analyze the role of AKT and Wnt signaling pathways in the regulation of IFNß expression and to identify genome sequences which are, like the IFNß locus, trapped in nuclear filaments formed by the Rift Valley Fever Virus non structural protein NSs. These projects are all in the continuity of the previous work of this team.

Strengths: The scientific level of the team's activity is good, regarding the size of the team in the last 4 years. The group published 4 publications, in Nucleic Acids Res, J. Cell Sci, Mol. Cell. Biol. and Plos Pathog. The team has developed a strong collaboration with two other French groups for the project on NSs protein of Rift Valley Fever Virus, which is supported by 2 ANR contracts (obtained in 2005 and 2008).

Weaknesses: There is currently no PhD student in the group, and only one has been graduated for the last 4 years. The international visibility of this group is very poor. Collaborations with foreign laboratories are limited, and the group leader never goes to international meetings to present their nevertheless interesting results.

Recommandations: The international visibility should be increased at least by the participation in international meetings, and the formation of PhD students is encouraged.

CHROMATINE, ORGANISATION SPATIALE DU NOYAU ET RÉGULATION DE L'EXPRESSION DES GÈNES EUCARYOTES

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	B	A

Group 2: Regulation of interferon-A gene expression in the antiviral and antitumoral innate immunity.

This team consists of two senior researchers (both CR1 CNRS) and has an ongoing strong collaboration with a Canadian laboratory (McGill University, Canada). The major focus of this team is to understand the mechanism by which interferon (IFN)-A genes are regulated upon virus infection in mouse and human cell lines. There are ten IFN-A genes clustered in the genome, all of which encode secreted proteins involved in innate and adaptive immunity. In particular, this team has been studying two members of the IFN regulatory factor (IRF) family, IRF-3 and IRF-7. Both are DNA-binding transcription factors which are activated by phosphorylation during viral infection by the kinases TBK1 and IKKe. The team utilizes reporter gene, electrophoretic mobility shift and chromatin immunoprecipation assays to study the differential regulation of various IFN-A genes by IRF-3 and IRF-7. They have found evidence in human cells that several IFN-A genes, which are activated by IRF-7 are repressed by IRF-3. To explore the possibility that IRF-7 acts by a different mechanism from IRF-3, the team proposes to screen for IRF-7 binding partners using two-hybrid technology and preparative immunoprecipitation followed by mass spectrometry. Targets of the IRF proteins will be identified by chromatin immunoprecipitation combined with microarray technology. Among other proposed projects are explorations of the histone modifications that occur at IFN-A promoters in response to viral infection.

Strengths: This team has a long-standing interest in IFN-A gene regulation and has shown willingness to tackle the complexities of the system. They have also taken advantage of their collaboration with the Canadian lab to publish high quality data (e.g. J. Biol. Chem. 281: 4856).

Weaknesses: Productivity is an issue, with the team publishing only two papers from 2004-2008, only one of which was corresponded by the group leader. It is not clear what insights will be gained from the examination of histone modifications on IFN-A promoters, as the epigenetic markers that will be tested are already known to correlate with gene activation. While the team has uncovered interesting examples of differential regulation of IFN-A genes by IRF-3 and IRF-7, it is not clear that they can provide any meaningful mechanisms to explain this complexity. The screens to identify IRF binding proteins and targets are ambitious and this team has no prior expertise in these techniques, raising doubt as to whether they can be successful.

Recommandations: This team is hampered by its small size and lab budget, and would benefit from the addition of students or post-docs. A large collaborative grant with the Canadian Institute of Health will be submitted in March 2009, but it is not clear whether it will be funded. The low productivity of the past four years is not unusual for this team, and may be all that can be expected for future periods.

RÉGULATION DE L'EXPRESSION DES GÈNES INTERFÉRON-A (IFN-A) AU COURS DE LA RÉPONSE IMMUNITAIRE INNÉE ANTIVIRALE ET ANTITUMORALE

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
C	C	C	C	C

Group 3: Genetic diseases-keratinocyte biology

The team is led by the director of the unit, consists of 10 people (3 permanent scientists, 1 assistant-professor, 1 postdoctoral scientist, 3 PhD students and 1 technician). Several independent goals are pursued in this group, while none of them can be designated as the main topic. The subjects include: 1) the evolutionary conservation of the involucrin gene of keratinocytes, 2) the role of transglutaminase in the production of intracellular protein inclusions in Huntington's disease, by formation of isodipeptidic [N-(γ-glutamyl)lysine] (iEK) covalent bonds, 3) the function of basonuclin-2, a protein identified in the group by its sequence homology to basonuclin-1, and which appears to be important for development of the craniofacial skeleton. Overall, the researches performed in this team reach at a good level and uses a panel of very diverse methods, like the in vitro culture of rodent keratinocytes, the determination of iEK isopeptide in brain extracts by HPLC and mass spectrometry, or the knock-out of the gene encoding basonuclin-2 in the mouse. Plans for the future are to continue parallel studies, on the one hand on the differentiation and proliferation of the keratinocytes and, on the other hand, on the pathological role of protein inclusions in neurodegenerative diseases. Protein aggregates characteristic of Huntington's and other neurodegenerative diseases will be analysed by mass spectrometry, to find out particularly if the presence of iEK could be used as a sensitive biomarker of these disorders. Study of the biological function of basonuclin-2 will be extended by focusing on its suspected role in the control of human mesenchymal cell and keratinocyte proliferation, with possible application in oncology, and by searching for protein partners of basonuclin-2 using affinity chromatography or immununoprecipitation techniques followed by mass spectrometry.

Strengths: The research performed in this team are both original and of worthy quality. Important scientific questions are addressed with cutting-edge technologies, taking the best advantage of the common facilities at the local institute (IFR 95) and the proteomic facility of Paris 5 (3P5). The group leader is a recognized scientist that managed to surround himself with talented young colleagues and develop national and international collaborations.

Weaknesses: Although the number and quality of publications in the last years were honourable, the team could be more ambitious and target when possible higher impact journals. It can be feared that the large scattering of the research topics will have on the long term a negative effect on deepening of the analyses and on scientific productivity.

Recommendations: The team should try to define more precisely its research domain and choose one essential subject on which to focus its expertise. This is a required condition to reach international notoriety. The group leader, who will be at the same time the head of the laboratory and the head of the Saint-Pères IFR of Neuroscience, will have to work very efficiently to combine his diverse responsibilities and continue to develop and optimize the research conducted in his team.

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A+	A

Group 4: Synthetic peptides for HIV-1 vaccine preparation and anti-cancer therapy

The head of this team is a senior researcher with a permanent CNRS DR1 position. It also includes a senior researcher (CR1 INSERM), two technicians and two Ph.D. students. The team leader presented two mains projects that have been pursued in the last years, since their arrival in 2004. The first one deals with the design of an HIV vaccine based on a synthetic peptide, CBD1, corresponding to the consensus caveolin-1 binding domain of gp41. Using different animal models, from mice to non human primates, the team has been able to demonstrate the induction of neutralizing antibodies when specific adjuvants are included in the formulation. Their specific project aims to first demonstrate the efficacy of this HIV vaccine candidate, either alone or in combination with other peptides derived from the same caveolin-1 motif, in non human primates and second, to characterize the neutralizing epitopes which could be recognized by the immune response induced, using mice experiments and monoclonal antibodies. The other main project concerns the anti-tumoral action of a pseudo peptide, HB-19, or its derivatives. Identified as a specific antagonist at the cell surface expressed nucleolin, this peptide has shown strong inhibition of angiogenesis and tumoral growth, using athymic nude mice activity and standard inhibitory activities. Next steps will consist to both explore more potent derivatives and to characterize molecular mechanisms involved.

Strengths: This team has a strong commitment to transfer their results to human application as it is illustrated with the numerous patents owned by the P.I. and by the exclusive license, which has been granted to a French start up for the development of HB-19 peptide (Nucant).

Weaknesses: Research program for the next years lacks of scientific perspective or rigor and may be too much "industry"-driven, and the team leader does not seem to be aware of the future of the team as it will be his last "quadriennal". Furthermore, quality of the results published or announced could be an issue, specifically results concerning the induction of heterologous neutralization antibodies directed against HIV primary isolates. The lack of clear external funding for the next four years could hamper both the go/no go decisions concerning the development of HIV vaccine candidates and anti-tumoral characterization of the B-19 pseudo-peptides analogues.

Recommandations: This team is quite isolated both at the lab space level and in the thematic of the unit. It would gain credibility to be included in current HIV networks, which are well aware of the results of this team and have already expressed their willingness to test the neutralizing capacities of the sera obtained through the immunization studies of this team. Existing collaboration with other groups of the unit are strongly encouraged, especially with regards to the future of the team. Addition of a post-doc or the arrival of a young researcher should be a way to maintain a long-term future for this team, which otherwise risks to be engaged in an uncertain future.

PEPTIDES SYNTHÉTIQUES COMME MOLÉCULES ANTITUMORALES ET VACCIN ANTI-VIH

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	A	B	B	B

Group 5: Steroid and beta-catenin signalling in glial cells: implications in myelinisation and neuropathies

This young and dynamic team of 6 persons has high scientific impact on the visibility of the unit. This group has made many interesting and noted observations on the crucial role of glucocorticoids as signalling molecules in the nervous system. The main recent finding of the group is that in Schwann cells the glucocorticoid receptor recruits beta catenin instead of the typical coactivator CBP.

Now the main objectives of the group are to investigate the role of the wnt/beta catenin pathway in the expression of myelin genes in Schwann cells and how this pathway converges with glucocorticoid signaling. Most of the studies are based on the combination of molecular, cellular and pharmacological approaches. The group also develops transgenic mice lacking specifically beta catenin in Schwann cells in collaboration with the Max Planck Institute in Gottingen. One of the strongest points of the group is the development of new biophysical techniques such as atomic force microscopy to show the impact of wnt signaling on Schwann cell shape modification. This facility is provided in house and benefits of an assistant professor s competences in biopysics.

The final aim of the group is to analyze the effects of glucocorticoids and beta catenin pathways in the progression of Charcot-Marie-Tooth pathology, which is the most frequent hereditary neuropathy with myelin disorders. In that context the group is currently generating, still in collaboration with Gottingen (Germany), transgenic rats with extra copies of the disease gene PMP22.

Strengths: Since 2006 when the group leader joined the unit, the team has substantially expanded by the arrival of an assistant professor, who allowed the development of new promising biophysical techniques. The group is also strengthened by the arrival of new post-doc and graduate students.

Weaknesses: In addition to their scientific activities, the group leader (professor) and the assistant professor have many teaching activities. Increasing the size of the group will be necessary to reach high achievement standards. Securing this development might be one of the priorities of the director.

Recommandations: The group is encouraged to publish in higher impact factor journals, to ensure higher scientific recognition and visibility for the group.

MÉCANISMES DE LA SIGNALISATION ET DE LA RÉGULATION TRANSCRIPTIONNELLE PAR LES RECEPTEURS NUCLÉAIRES ET LA VOIE WNT/B-CATÉNINE DANS LES CELLULES GLIALES

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	A	A

5 • Appreciation of resources and of the life of the research unit

This is a rather small unit (30 people in total) with five groups, dispersed in two different floors of the IFR, where another 13 units function.

There has been gradual erosion in institutional funding, which should be closely monitored by the CNRS since a continuation of this trend will significantly reduce competitivity of the unit as a whole. 80 % of the unit's budget comes from outside grants.

Discussion with PIs, tenured staff, technical and administrative staff, post-doctoral and doctoral students indicated a good degree of cohesion and interaction within the unit and a general contentment in the way in which the unit functions.

6 •Recommendations and advice

— **Strong points:**

In general the scientists and the staff are happy to work in the unit. A clear strength of the unit over the past years has been its ability to attract a young energetic group leader and several post-docs and staff scientists who wanted to join the unit and/or come back to France. The unit has filed a relatively large number of patents.

— **Weak points:**

The unit has limited international visibility. In certain groups very few Ph.D. students and post-doctoral fellows are hired. The groups are dispersed in two floors amongst the other 13 units of the IFR. There is little coherence amongst the projects suggested by the five groups. In the plan presented for the next four years, the groups did not really coordinate their future research fields to connect better to each other. Some of the presented projects lack sufficient focus. The committee noticed that certain groups lack international collaborations and very few of the groups participate in EU grants. The unit has no "council of laboratory" (conseil de laboratoire).

— **Recommendations:**

The committee thinks that the unit should increase its visibility and recruit more Ph.D. students and foreign post-docs. Most of the PIs of the unit should focus better their projects and also write more grants to attract more outside funding (containing salaries for students and post-docs). The PIs should try to publish their studies in more visible, higher impact journals. Students and post-docs are encouraged to be actively involved in the life of the unit, through a variety of activities. All the scientists (including PIs, post-docs and PhD students) are strongly encouraged to participate in internationally important meetings of their field.

The committee thinks that the unit is viable and that the support should be maintained. The management should be given the appropriate tools and resources to re-enforce the actual qualities and implement novel research avenues. Creating a larger unit (by unifying some of the existing ones in the IFR with similar thematic) would help to increase the impact of the research at the national and international level.

Régulation de la transcription et maladies génétiques

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	A	B	B	B

UNIVERSITÉ
PARIS DESCARTES

Le Président
Axel KAHN

Paris, le 1er avril 2009

DRED 09/n° 130

Monsieur Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'unité « **UPR 2228 Régulation de la transcription et maladies génétiques** » rattachée à mon établissement.

Je partage l'étonnement des chercheurs de l'unité devant la sévérité de certains jugements portés par le comité de visite. Je souhaite que l'AERES tienne le plus grand compte de la réponse argumentée de son directeur. L'Université veillera bien entendu à ce que les remarques qui lui ont été adressées pendant la visite, notamment quant aux difficultés matérielles rencontrées par cette unité, soient prises en considération.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma meilleure considération.

Le Président de l'Université

Axel Kahn

Université Paris Descartes 12, rue de l'Ecole de Médecine 75270 Paris Cedex 06
Tél. 33(0) 1 40 46 16 01 Fax 33(0)1 40 46 16 43
Email : axel.kahn@parisdescartes.fr

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

***UPR 2228** - Régulation de la Transcription et Maladies Génétiques*

Philippe DJIAN
Directeur

UNIVERSITÉ PARIS DESCARTES

REPONSE AU COMITE DE VISITE AERES DU 6 FEVRIER 2009

We thank the AERES committee for its report and we will undoubtedly take into account the recommendations of the committee. A recurrent criticism in the AERES document is that our unit is too small and should try to fuse with some of the local labs in order to form a larger unit with more international visibility. We have explored such possibilities in the past. However the IFR to which we belong is characterized by its heterogeneity in terms of research subjects: it associates neurosciences with toxicology, pharmacology and chemistry. While this could be considered as a strong point because it favors interdisciplinary approaches to biological questions, it does not favor the fusion into a large unit. With the new organization of the Université Paris Descartes along research disciplines rather than geographical location, new opportunities might emerge in terms of our participation in a larger structure.

We wish to express our disagreement with the AERES report on two points:

1. That very few of our papers appeared in high impact factors journals
2. The comments on Ara Hovanessian's research (see also specific answer below)

1. **Very few (papers) appeared in high impact factors journals**: The AERES committee implies here that good research is published in high impact journals and therefore presumably that bad research is published in low impact journals. Thus it is a good thing to publish in high impact journals. The committee should be aware of the countless examples of very original research published in low impact journals and vice versa of rather poor results (to say the least) reported in high impact journals. We wish that scientific committees in general would evaluate a research group on the merits of its research rather than simply recite the impact factors (IF) of the journals in which the evaluated group has published.

It is not clear to us what a "high impact factor journal" is for the AERES. The only element that we could find was on page 3 of the document on "criteria of identification of publishing scientists", where the JBC is referred to as a journal of "high audience". It is explained there that a single paper as first author over a four-year period is sufficient to qualify a scientist as "publishing". Using this definition, we discovered that, contrary to the committee's statement, we have published a fair number of papers in high impact journals. If we take the impact factor of the JBC as threshold (IF=5.5-5.6 over the recent period), we find that between August 2004 and August 2008 (time of completion of the document sent to AERES), we have published **17 papers in journals with a high impact factor; 15 of these papers resulted either entirely or**

UPR 2228 - Régulation de la Transcription et Maladies Génétiques
Université René Descartes
45, rue des Saints-Pères - 75270 PARIS Cedex 06
Téléphone 33 (0)1 42 86 22 72 - Télécopie 33 (0)1 42 60 55 37 - Adresse électronique philippe.djian@univ-paris5.fr

Philippe DJIAN
Directeur

predominantly from work performed in our unit. **Is this very few for a unit of our size?**
These papers were published in the following journals:

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Université René Descartes
45, rue des Saints-Pères - 75270 PARIS Cedex 06
Téléphone 33 (0)1 42 86 22 72 - Télécopie 33 (0)1 42 60 55 37 - Adresse électronique philippe.djian@univ-paris5.fr

- Immunity (IF=19.3): 1 paper (A. Hovanessian)
- Endocrine Rev (IF=18.5): 1 paper (C. Massaad)
- PNAS (IF=10.4): 3 papers (P. Djian: 2, C Massaad: 1)
- J. Cell Biol. (IF=9.6): 1 paper (P. Djian)
- PLoS pathogens (IF=9.4): 1 paper (E. Bonnefoy)
- Cancer Res. (IF=8.0): 1 paper (C. Massaad)
- Nucleic Acids Res. (IF=7.0): 1 paper (E. Bonnefoy)
- Mol. Cell. Biol. (IF=6.4): 2 papers (S. Navarro, E. Bonnefoy)
- J. Cell Sci. (IF=6.4): 1 paper (E. Bonnefoy)
- J. Biol. Chem. (IF=5.6): 3 papers (A. Hovanessian, A. Civas, P. Djian)
- Mol. Endocrinol (IF=5.5): 2 papers (C. Massaad).

2. **Comments on Ara Hovanessian's research**: The committee stated that Ara Hovanessian is "a senior researcher". This is true, but the committee could also have said that Ara Hovanessian is a very distinguished scientist. The AERES seems to be very preoccupied with the impact factor of journals and with various fancy methods of estimating a scientist's productivity. Here are some bibliometric facts about Ara Hovanessian:

- Total number of papers: **235**
- Papers in Cell, Nature or Science: **9**
- Papers in Immunity, EMBO J and PNAS: **11**
- Papers with an IF between 5 and 10: **55**
- Total number of citations: **5,839**
- H-Factor: **57**

In view of these bibliometric data, it is quite surprising to read among the committee's comments on Ara Hovanessian that "quality of the results published or announced could be an issue". Obviously, the authors of the nearly 6.000 papers that have cited Ara Hovanessian's work did not think that quality of the results was an issue, otherwise they would not have cited him. It could be assumed that if somebody has published reliable data in the past, he will continue to do so in the future.

It is rather unpleasant to read vague insinuations on a researchers's work in a document that is going to become public. We would have appreciated that the committee made specific comments on the aspects of Ara Hovanessian's results on which it disagreed rather than unfocussed disparaging remarks. It is also worth noting that the AERES evaluation is somewhat in contradiction with that of other international and national expert scientific committees who have in the last four years:

- Granted Ara Hovanessian over 500 k€ in research funds
- Issued two press releases (CNRS and Immunity in 2004; CNRS and PLoSONE in 2008)
- Licensed various patents
- Extended numerous invitations to conferences
- Accepted his papers in well-known journals

Specific answers for Team 1

We agree with the AERES committee on the need to increase the international visibility of the team and on the necessity to hire new PhD students. Two M1 and one M2 students have joined the group this year and we hope that the PhD project presently submitted to the Doctoral School "Complexité du Vivant" (University Paris 6) will lead to a PhD recruitment. The group leader will be attending this year Cold Spring Harbor Meeting on Mechanisms of Eukaryotic Transcription (August 25-29).

Nevertheless, we want to point out that the overall situation of the team concerning these two points has not been as weak during the last years as stated by the AERES committee:

-While the group leader has priviliged the participation at national conferences, the other members of the group have attended and presented their results at prestigious international meetings such as EMBO Conference on Chromatin and Epigenetics and Keystone Symposia on Chromatin Dynamics and Higher Order Organization.

-An international collaboration was developed with the group of Ricardo Maccioni, director of the Laboratory of Cellular, Molecular Biology and Neurosciences at the University of Chile. In the context of this collaboration, a Chilean PhD student came to France to do research in our group and the results obtained during this collaboration were published in J. Cell Sci. in 2006.

-The group has been regularly forming M1 as well as M2 students. Even though unfortunately this has not resulted in recent PhD student recruitments, the work carried out by M2 students has contributed in an important way to the group's scientific production with several of these students being among the authors of the group's publications.

Specific answers for Team 2

We thank the members of the AERES Committee who have recognized our long-standing interest in IFN-A gene regulation and our willingness to tackle the complexities of the system. The Committee also points out our publication of high quality data, our international visibility and our ongoing strong collaboration with an international leader in the regulation of innate immune response signaling (McGill University, Canada). However, the Committee criticizes the low productivity of the team due to its small size and low budget.

Team members request that the Committee take into consideration the publication that was sent for revision before the AERES Committee meeting and that has now been accepted at Molecular and Cellular Biology (see annex 1). One team member is the first author and the other is the corresponding author of this publication under revision in a high quality journal.

Concerning the budget, Team 2 studies will be supported in 2009 by a collaborative agreement (15,000€, n° 23631-CNRS) with McGill University. The team has also applied in March 2009 for a collaborative operating grant of the Canadian Institutes of Health Research (total of 100,000 $ per year). This application is entitled "Small molecule agonists of the RIG-1 pathway as innate stimulatory agents against influenza virus infection". It is based on our preliminary results on histone H3 marks associated with actively transcribed *ifn-a* genes, as

well as the on the potential role of IKK-ε on Serine 10 phosphorylation of histone H3 and in tumor progression. The decision for this application is due in June 2009.

Concerning students, the team will work with two Master1 students and one Master2 student from April to July 2009. Additionally, we submitted a project in March 2009 at the G2ID doctoral school for a doctoral fellowship from the ministry.

The team members were surprised by the severity of AERES members comments on the projects dealing with histone modifications on IFN-A gene promoters, and mechanisms explaining the complexity of differential regulation of IFN-A genes. The team has provided evidence that the regulation of human *ifn-a* gene expression is tightly controlled by IRF3, synergizing with IRF7 in a first step, but also exerting an inhibitory effect on IRF7-mediated transcription of a majority of *ifn-a* genes, in a second step. Dual transcriptional role of IRF3 provides an explanation for the differential expression of *ifn-a* genes in various cells following virus-activated signaling. Additionaly, their preliminary data, presented to the committee, indicate that the high expression of *ifn-a* genes is linked to IKK-ε-activated Serine 10 phosphorylation of histone H3 associated to *ifn-a* gene promoters. An essential finding is that this modification is observed when IKK-ε activates IRF7, but not when it activates IRF3. The kinase responsible for Serine 10 histone H3 phosphorylation is unknown in the case of *ifn-a* and *ifn-b* gene transcription, although it is recognized that this phosphorylation is a key mark linked to other modifications (acetylation and methylation) of histone H3. In this regard, comparison of histone modifications induced by IKK-ε in the presence of IRF3 or IRF7 is necessary for providing new insights on differential regulation of *ifn-a* gene family members that occupy the same locus of 400 kb on human chromosome 9. Determination of "epigenetic markers already known to correlate with gene activation" constitutes a first part of the project, the other consisting on the identification of new markers related to virus-activated signalings mediated by IRF3 and IRF7.

The Committee stated that the screens to identify IRF7 binding proteins and targets are ambitious, and raised doubts as to whether the team members will be successful since they have no prior expertise in these techniques. The team proposes to identify IRF7-interacting partners by using two-hybrid technology and to determine new targets (gene promoters) for IRF7 by ChIP-on-chip analysis. The team members contacted an expert group at the Institut Pasteur for the two-hybrid system. They have informed the Committee about their contact with the head of a transcriptome platform, with a recognized expertise in ChIP-on-chip technology. Use of new technologies has not discouraged the team members in the past, and we do not see why it should in the future.

Specific answers for Team 4

This review on the research activities of Team 4 is full of contemptuous and unjustified remarks against the Team leader Ara Hovanessian, who is a well-recognized scientist at the international level and respected for his important contributions in the fields of interferon and HIV.

As was stated clearly in our report, the aims of our research projects are 1) the development of a synthetic peptide vaccine against HIV and 2) the antitumoral action of pseudopeptides targeting surface nucleolin. It is curious that the committee has focused entirely on he HIV work and has ignored entirely our project on the use of HB-19 as a novel anti-cancer treatment. The anti-cancer effect of HB-19 attracted worldwide attention in 2008 (press release by CNRS

and PLoSONE) and represents a substantial fraction of the research that we intend to carry out in the next four years.

During the period 2004-2008, the team has published 15 papers in good quality journals including Immunity, J. Biol. Chem., Molecular Immunology (2 papers), PLoS ONE, Eur. J. Biochem., Exp. Cell Res., FEBS J., and BMC Microbiol. In addition, four CNRS patents, 1 INSERM patent and several CNRS «Declarations d'Inventions» were filed. The team benefited from 520,000€ in grants obtained from the American Foundation for AIDS Research, the ANRS, the SIDACTION and the ANR.

Strengths: Besides an ironical comment on the patent applications, strangely there is not a single word on the high quality work achieved by the team of Ara Hovanessian in the last few years. For instance, the Phase I trials on Nucant pseudopeptides will be conducted in a few months by ImmuPharma, which is a company with shares at the London Stock Exchange.

Weaknesses: This section is full of ill-willed remarks that require clarification individually.
1. "Research program **lacks scientific perspective** or **rigor** and may be **too much industry-driven**….." It is difficult to state that the program lacks scientific perspective when the aim of this team is on one hand the **development of specific immunogens for an efficient vaccine preparation against HIV/AIDS** infection, and on the other hand the demonstration that HB-19 and related Nucant pseudopeptides represent **novel therapeutic opportunities in treatment of a wide variety of cancers and related malignancies**.
- "**rigor**": this is meaningless considering the high quality research achievements of Ara Hovanessian as evidenced by his numerous publications throughout the years.
- "too much industry-driven": To characterize multiple functions of surface nucleolin in adhesion, metastasis, transformation, inflammation, and selective cell killing of leukemia cells is **a long-term project, which is mostly fundamental research**.

2. "**The team leader does not seem to be aware of the future of the team….**" Again it is strange to see such an insinuating statement on a DR1 CNRS who has been a successful group leader since 1980. Ara Hovanessian has still 7-8 years before retirement.

3. "**Furthermore, the quality of the results published or announced could be an issue, ….. neutralizing antibodies directed against HIV……..**": This is indeed an insulting statement not only towards Ara Hovanessian but also against the international scientist-experts who had reviewed the work that was published in **Immunity**, and in two papers in **Molecular Immunology.** Concerning the "**announced results**" this work is recently accepted for publication in **Vaccine** with highly enthusiastic recommendations made by three independent reviewers. Moreover, the HIV-vaccine project has been very well considered by several international and national scientific HIV-committees as evidenced by the several grants obtained since 2004: SIDACTION 38K€, amfAR 80K€, ANRS 130K€, and ANRS 210K€.

4. "**The lack of funding for the next four years**": The current evaluation for the efficacy of the CBD1 peptide vaccine mixture in macaques is supported by an ANRS grant of 140.000€. The results of this study should be available by the end of 2009 thus permitting the application of a new grant to ANRS for the period of 2010-12. As far as the Nucant project, Ara Hovanessian has already participated in a meeting with CNRS officials and the management of ImmuPharma for a research contract between his team and ImmuPharma based on the recent findings. This will be a contract for three years with a budget of 40-50K€ per year.

Recommendations:

"**It would gain credibility to be included in current HIV networks**": ANRS director and/or officials nominate researchers in various HIV networks including vaccine trials. Although Ara Hovanessian had obtained several ANRS grant, he has never been asked to join one of these networks.

"**Testing the neutralizing activity of the immune sera by other groups**": The neutralizing activity of the immune sera is tested using the physiological target cells of HIV-infection, i.e. primary $CD4^+$ T lymphocytes, in contrast to the "other groups", which use artificial experimental cell models for HIV infection.

We have previously reported that while anti-CBD1 immune sera manifest HIV-1 neutralizing activity in primary $CD4^+$ T lymphocytes, these same immune sera have very little or no effect in cell-experimental models designed for HIV infection. This restriction appears to be associated with the action of anti-CBD1 immune sera on gp41 (transmembrane envelope glycoprotein), since antibodies directed against gp120 (surface envelope glycoprotein) have the capacity to neutralize at similar extend both primary $CD4^+$ T lymphocytes and other cell types. This difference between anti-gp41 and anti-gp120 neutralizing antibodies is most probably the consequence of the complex mechanism of gp41 mediated fusion process between viral and cellular membranes, which might also be due to differences in the plasma membranes between cells.

Philippe Djian

ANNEX 1

De : mcb@umich.edu
Date : 28 mars 2009 16:58:30 HNEC
À : ahmet.civas@univ-paris5.fr
Objet : Decision on manuscript MCB01805-08 Version 2

Dr. Ahmet Civas
UPR2228 - CNRS
UFR Biomédicale des Saints-Pères, Université Paris5
45 rue des Saints-Pères
Paris 75270
France

Re: Differential Regulation of Human Interferon-A Gene Expression by Interferon Regulatory Factors 3 and 7 (MCB01805-08 Version 2)

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James Douglas Engel
Editor, Molecular and Cellular Biology (MCB)

Journals Department
American Society for Microbiology
1752 N St., NW
Washington, DC 20036
journalsrr@asmusa.org
1-202-942-9214
1-202-942-9355